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(21) International Application Number: PCT/GB99/01195 (22) International Filing Date: 19 April 1999 (19.04.99) (30) Priority Data: 9808229.0 17 April 1998 (17.04.98) GB (71) Applicant (for all designated States except US): QUADRANT HOLDINGS CAMBRIDGE LIMITED [GB/GB]; 1 Mere Way, Ruddington, Nottingham NG11 7JS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAN, Roger, Antonius, Henricus [NL/NL]; Dept. of Medical Pharmacology, Rudolf Magnus Institute for Neurosciences, Utrecht University, Universiteitsweg 100, NL-3508 TA Utrecht (NL). GISPEN, Willem, Hendrik [NL/NL]; Dept. of Medical Pharmacology, Rudolf Magnus Institute for Neurosciences, Utrecht University, Universiteitsweg 100, NL-3508 TA Utrecht (NL). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MELANOCORTIN RECEPTOR LIGANDS (57) Abstract Peptides (many of which are novel) interact selectively with melanocortin receptors, particularly the MC3, MC4 and MC5 receptors. The peptides have been characterised <i>in vivo</i> , and shown to have an effect upon behaviour or metabolism.		

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MELANOCORTIN RECEPTOR LIGANDS

Field of the Invention

The present invention relates to peptides which interact selectively with melanocortin (MC) receptors and which have been characterised *in vivo*.

5 Background of the Invention

The melanocortins were originally described as mediators of pigmentation. For example, US-A-5674839 and US-A-5714576 disclose cyclic and linear analogues of α -MSH for stimulating melanocytes in vertebrates to treat hypopigmentation disorders. One such known peptide is Ac-Ser Tyr Ser Nle c[Asp His D-Phe Arg Trp
10 Lys] Gly Pro Val-NH₂.

Melanocortins are now known to modulate neurophysiological and neuropathological phenomena such as conditioned avoidance, central control of autonomic systems, different types of behaviour (grooming, female sexual behaviour, anxiety, aggression), drug addiction and nerve regeneration (De Wied and Jolles,
15 Physiol. Rev. (1982) 60:976-1059). The demonstration of binding sites for melanocortins in the brain (Tatro, Brain Res. (1990) 536:124-132) and the cloning of brain-specific MC receptors (Mountjoy *et al*, Mol. Endocrinol. (1994) 8:1298-1308; Chhajlani *et al*, Biochem. Biophys. Res. Commun. (1993) 195:866-873; and Reh fuss-Roselli *et al*, Proc. Natl. Acad. Sci. USA (1993) 90: 8856-8860) further
20 underscored the significance of the brain melanocortin system. A number of distinct receptor sub-types have now been shown to be expressed in the brain.

Although the precise function of each sub-type has yet to be determined, it is clear that the receptors are important in many regulatory mechanisms. For example, the MC3 receptor has been implicated in increasing blood pressure and heart rate,
25 whereas the MC4 receptor is believed to decrease blood pressure and heart rate. In addition, the MC4 receptor is believed to be a mediator of melanocortin - induced grooming. The receptors may also play a role in nerve regeneration, as treatment with melanocortins has been shown to enhance maturation of the nervous system. In particular, the MC4 and MC5 receptor may be important in this process.

30 The deletion of the MC4 receptor gene from mice and the identification of certain endogenous antagonists have shown that the MC4 receptor may be implicated in the brain melanocortin system regulation of weight homeostasis (Shutter *et al*, Genes Dev. (1997) 11: 593-602; Huszar *et al*, Cell (1997) 88: 131-141). However, the exact involvement of the melanocortin system in neurophysiology and weight

homeostasis is not yet fully understood. Likewise, the mechanisms underlying the effects of melanocortins on the diverse brain functions described above are unknown. Nevertheless, a number of ligands for MC receptors are known. α -Melanocyte-stimulating hormone (α -MSH) is a linear tridecapeptide which is involved in the regulation of skin pigmentation and has various actions on the brain which affect behaviour. In the brain, α -MSH has been shown to interact with several melanocortin receptors, such as MC3, MC4 and MC5. In addition, some α -MSH analogues, such as cyclic lactam analogues, have been shown to be agonists of MC receptors activating both MC1 receptor activity and other MC receptors.

Although some *in vivo* data is available for MC receptor ligands, *in vivo* activity is poorly characterised. Peptide activity *in vivo* has been assessed, for example, in rats by means of a grooming assay. The stretching and yawning syndrome (Ferrari, Nature (1958) 925-926) and grooming behaviour in the rat (Gispen *et al*, Life Sci. (1975) 17: 645-652) were among the first described behaviours which are under the control of the melanocortins. Grooming behaviour consists of activities directed to the animal body surface like face washing, body grooming, licking, scratching and genital grooming. Grooming behaviour is thought to be under control of the MC4 receptor (Adan *et al*, Mol. Pharmacol. (1994) 46: 1182-1190).

Despite some *in vitro* binding analysis, there is still a need for the provision of peptides which have a family for specific MC receptors, particularly MC3, MC4 and MC5 receptors, and whose activity has been characterised *in vivo*.

Summary of the Invention

According to the present invention, peptides have been identified which, surprisingly, exhibit differential binding to the MC3, MC4 and MC5 receptors, and which exhibit biological activity *in vivo*. The peptides are modifications of the α -MSH peptide and show distinct neurophysiological effects that are manifested as behavioural patterns.

In a further aspect of the invention, the peptides are useful to mediate physiological effects controlled or affected by the MC3, MC4 and MC5 receptors, including metabolic and behavioural changes. The invention, thus, extends to include pharmaceutical preparations containing the peptides, and methods of treatment which involve the use of the peptides.

Peptides according to the present invention are:

- (i) Ac-Nle c[Asp His D-Tyr Arg Trp Lys]-NH₂;

(ii) Ac-Ser Tyr Ser c[Cys Gly His D-Phe Arg Trp Cys] Lys Pro Val-NH₂;

(iii) Ac-Tyr Val Nle Gly His Phe Arg Trp Asp Arg Phe Gly-NH₂; and

(iv) Ac-c[Cys Gly His D-Nal Arg Trp Cys]-NH₂.

In addition, the peptide:

5 (v) Ac-Ser Tyr Ser Nle c[Asp His D-Phe Arg Trp Lys] Gly Pro Val-NH₂ may be used to treat various disorders in which the melanocortin receptors are implicated.

"Ac" represents acylation, and "c[]" represents a cyclic structure. "Nle" represents the oxidatively stable isostere for methionine.

A preferred peptide is (iii) which has good selectivity for the MC3 receptor as opposed to the MC4 receptor.

Description of the Invention

The peptides may have many uses in therapy. In particular, the peptides may be used in the manufacture of compositions for therapy (including prophylaxis where relevant) of neurological disorders including memory deficit and nerve damage, behavioural disorders including compulsive behaviour, stress, anorexia and addiction, cardiovascular disorders including cerebrovascular disorders such as stroke, metabolic disorders including obesity, sexual dysfunction including erectile dysfunction, or inflammatory events such as pain and fever.

20 The peptides may also be used to prevent or reduce nerve damage, e.g. as caused by other drugs or chemotherapy. They may therefore be co-administered with, say, cytotoxic agents.

The peptides of the present invention may be administered by any suitable means, many of which will be apparent to the skilled person. For example, the peptides may be administered orally, buccally or transdermally, or by the intravenous, intramuscular, pulmonary, mucosal, rectal or subcutaneous route. The formulation of the peptides into suitable compositions for delivery, will be apparent to the skilled person. For example, it will be readily apparent which pharmaceutically acceptable excipients or diluents are appropriate.

30 The amount of peptide to be delivered may be determined by the route of administration, the extent of damage to be treated, and the relative activity of the peptide. Suitable amounts, and other relevant factors, can be determined by a skilled person.

The present invention will now be discussed with respect to the following, illustrative Examples.

Example 1 Synthesis of Peptides (Table 1)

The peptides shown in Table 1 were synthesised using F-Moc synthesis (Fields *et al*, Pept. Res. (1991) 4:95) on solid phase.

Peptides identified as MT-II, D-Tyr-MT-II, RM12004 and SHU 9119 (SEQ ID Nos 3, 4, 6 and 8 respectively) are cyclised *via* the side chains of Asp and Lys. Cyclisation was carried out in solution using Py-BOP. A 30 mmol scale was used with double coupling steps of 30 min and 4 equivalents of amino acid. Py-BOP (26 mg, 50 mmol) was dissolved in 20 ml of peptide grade DMF. Diisopropylethylamine (DIEA, 17 ml, 100 mmol) was added, followed by 20 mg (12 mmol) of deprotected peptide; the reaction was followed by HPLC analysis and found to be complete after 1 hour. The reaction was stopped after 2 hours, and the product purified using preparative HPLC.

Peptides identified as RMI 2001 and RMI 2005 (SEQ ID Nos. 5 and 9, respectively) are cyclised *via* disulphides. For example, the deprotected peptide of SEQ IS No 5 was dissolved in 40 ml of 0.5% NH_4HCO_3 (pH 8). After 24 hours, no free sulphhydryl could be detected by Elmanns reagent, and the solution was acidified with acetic acid. The product was lyophilised and purified using preparative HPLC.

Example 2 Receptor binding activity of peptides

Transfected HEK 293 cells (transfected with the rat MC3 or rat MC4 receptor) were grown in poly-L-lysine (Sigma) coated 24 well Costar plates. Two days after transfection, the cells were incubated with 100,000 cpm of ^{125}I -NDP-MSH (final concentration 0.1-0.2 nM) and various concentrations of peptides in Ham's F10 medium (Gibco) pH 7.4 containing 2.5 mM CaCl_2 , 0.25% BSA, 10 mM Hepes and 50 mg/ml (150 KIU/ml) aprotinin. After incubation for 30 min at room temperature, the cells were washed twice with ice-cold TBS containing 2.5 mM CaCl_2 and lysed in 1M NaOH. Radioactivity of the lysates was counted in a Packard Cobra γ -counter.

Table 2 (below) shows the corrected IC_{50} value (K_i) of these peptides on the rat MC receptors MC3-R and MC4-R. The peptides NDP-MSH, RMI-2001, Nle- γ -MSH, RMI-2004, RMI-2005, SHU9119 and MT-II all had an affinity on the rat MC3-R in the low nanomolar range, whereas α -MSH had an affinity which was 2-10 fold lower. [D-Tyr]-MTII had an affinity in the submicromolar range. α -MSH had a similar affinity on the rat MC4-R as compared to the rat MC3-R.

NDP-MSH and MT-II had affinities in the low nanomolar range on the rat MC4-R, similar to the affinity for MC3-R. However, in contrast to their affinity for the

rat MC3 receptor, RMI-2001, RMI-2005 and SHU9119 had affinities in the subnanomolar range for the rat MC4-R, and [D-Tyr]-MTII had an affinity in the low nanomolar range on the rat MC4-R. Thus, RMI-2001, [D-Tyr]-MTII, RMI-2005 and SHU9119 had an affinity on the rat MC4-R which is significantly higher as compared to the rat MC3-R. In contrast, Nle- γ -MSH and RMI-2004 had an affinity which is lower on the rat MC4-R as compared to the rat MC3-R.

Example 3 *in vitro* activity assay of receptor binding

Functional activity was assayed by the reporter activity of a LacZ gene, which is expressed under the control of a cAMP regulated promotor in a pCRElacZ construct to detect changes in intracellular cAMP as a result of receptor activation (Chen *et al*, Anal. Biochem. (1995) 226: 349-354). 293 HEK cells expressing either the rat MC3 receptor (Rehfuss-Roselli *et al*, *supra*) or the rat MC4 receptor (Alvaro *et al*, Mol. Pharmacol. (1996) 50:583-591) were grown in modified Eagle's medium (DMEM) supplemented with 10% FCS. MC-receptor expressing cells were transfected with 10 mg of the pCRElacZ construct using the calcium phosphate precipitation method. 20 hours after transfection, the cells were split into 96-wells plates. The next day, cells were treated for 6 hours with melanocortin receptor ligands in DMEM supplemented with 0.5% BSA and 25 mM HEPES (pH7.4). The agonist activity was measured by stimulating the cells with varying concentration of α -MSH, NDP-MSH, MT-II and RMI-2001, Nle- γ -MSH, [D-Tyr]-MTII and RMI-2004. After treatment, cells were lysed in PBS with 0.1% Triton X-100, frozen, thawed and assayed for β -galactosidase activity. The results are also shown in Table 2. In addition, antagonist activity was demonstrated with a fixed concentration of agonist and increasing concentrations of antagonists SHU9119 and RMI-2005. The antagonists were also screened for (partial) agonistic activity.

NDP-MSH, MT-II and RMI-2001 were the most potent ligands on the rat MC4-R, having EC₅₀ values of less than that 0.1 nM. α -MSH and RMI-2004 had comparable activities on the rat MC4-R which were in the (sub)nanomolar range [D-Tyr]-MTII had a subnanomolar EC₅₀ value and Nle- γ -MSH had an EC₅₀ value of 11 nM. On the rat MC3-R, only NDP-MSH and MT-II had a subnanomolar EC₅₀ value. RMI-2001, Nle- γ -MSH and RMI-2004 had EC₅₀ values in the low nanomolar range, whereas [D-Tyr]-MTII had an EC₅₀ value of 20 nM. Thus, MT-II, RMI-2001 and [D-Tyr]-MTII showed the highest difference between rat MC3-R and MC4-R, the

activity being higher on the rat MC4 receptor. Only Nle- γ -MSH was more potent on the rat MC3-R than on the rat MC4-R.

Partial agonistic activity on the rat MC3 receptor was observed for SHU9119 (maximal at 10 nM being 40% of maximal activity) and RMI-2005 (maximal at 40 nM being 25 % of maximal activity). RMI-2005, but not SHU9119, had also partial agonistic activity on the rat MC4-R, being 20 % of maximal receptor activation at 20 nM.

Example 4 *in vivo* activity of peptides administered cerebrally

Male Wistar rats weighing 120- 130 g were used. Rats were housed in single cages in a light-dark cycle of 12 h. Cannulas made from polypropylene tubes were implanted into the foramen intraventriculare under anaesthesia (Brakkee *et al*, Lab. Animal Sci. (1979) 29: 78-81). Rats were allowed to recover for 3 days and used for experiments during the next 10 days. Peptides dissolved in 3 ml of saline (154 mM NaCl) were injected intracerebroventricularly (i.c.v.) by means of a Hamilton syringe.

Grooming tests were performed according to (Gispen *et al*, *supra*). Briefly, rats were transported to an observation room at least 1 hour before start of the test. Grooming was induced either by agonist injection or by exposure to a novel environment which consisted of a Plexiglass box (30 cm/15 cm/15 cm) covered with a metal cover in which naive rats were kept during observation. Rats were placed into the observation boxes immediately after the injection. Observation started 15 min after the injection and continued for 50 min. Grooming was scored each 15 sec over 50 min, thus the maximum grooming score for a rat is 200. Rat activities such as vibration, face washing, genital grooming, body licking, scratching were considered as grooming. Each experimental group consisted of at least 6 rats.

Figures 1a and 1b are graphs of grooming score against agonist, and show the results of the grooming experiments. α -MSH, NDP- α -MSH, RMI-2001, [D-Tyr]-MTII, RMI-2004 and MT-II induced grooming after i.c.v. injections, whereas Nle- γ -MSH did not. Also RMI-2005 and SHU9119 did not induce grooming behaviour even at the highest tested dose of 1 nmol. RMI-2001, NDP- α -MSH and MT-II had similar potency with submaximal doses between 2 and 10 pmols. The lowest dose of these peptides that significantly increased grooming as compared to saline treated rats was 1.5 pmol for NDP- α -MSH and RMI-2001 and 4.5 pmol for MT-II. Thus, the three most potent MC4 receptor agonists were also the most potent peptides in inducing excessive grooming behaviour. Furthermore, the pharmacological profile of

melanocortin-induced grooming fits best with that of the rat MC4-R and not with that of the rat MC3-R. For instance Nle- γ -MSH is more potent and [D-Tyr]-MTII is less potent than α -MSH on the rat MC3-R, but [D-Tyr]MT-II is more potent than α -MSH on induction of grooming behaviour, whereas Nle- γ -MSH did not induce grooming.

5 **Example 5** *in vivo* activity of peptides administered intravenously

For intravenous injections via the tail, peptides were dissolved in 100 ml saline. Rats were injected intravenously with 100 mg α -MSH, NDP-MSH, MT-II, D-Tyr, RMI-2001 or RMI-2004, and grooming behaviour was observed. MT-II potently activated grooming behaviour, whereas NDP-MSH, D-Tyr, MY-II and RMI-2001
10 significantly stimulated grooming behaviour although to a lesser extent. RMI-2004 and α -MSH did not stimulate grooming behaviour.

Example 6 Peptide binding to mouse MC5 receptors

A number of ligands were screened for binding to the mouse MC5 receptor. IC50 values were determined according to the method given in Example 2. The
15 results are given in Table 3.

Table 3

Peptide	Receptor	IC50
RMI-2001	Rat MC5	2.7 e-07
RMI-2004	Rat MC5	1.5 e-09
RMI-2005	Rat MC5	3.6 e-09 (agonist)

20 **Example 7** Peptide binding to the human receptors

A number of ligands were screened for binding to the human receptors, including the human MC5 receptor. IC50 values were determined according to the method given in Example 2. The results are given in Table 4.

Table 4

Peptide	Receptor	IC50 value
RMI-2001	Human MC3	7.5 e-09
	Human MC4	5.6 e-09
RMI-2004	Human MC3	1.5 e-09
	Human MC4	9.7 e-09
D-Tyr-MTII	Human MC3	4.4 e-07
	Human MC4	2.8 e-08
	Human MC5	1.1 e-09
RMI-2005	Human MC3	1.4 e-08
	Human MC4	1.3 e-09
	Human MC5	1.9 e-07 (agonist)

Table 1

α -MSH	SEQID No 1	Ac-	Ser	Tyr	Ser	Met	Glu	His	Phe	Arg	Trp	Gly	Lys	Pro	Val	-NH ₂
NDP-MSH	SEQID No 2	Ac-	Ser	Tyr	Ser	Nle	Glu	His	D-Phe	Arg	Trp	Gly	Lys	Pro	Val	-NH ₂
MT-II	SEQID No 3				Ac-	Nle	c[Asp	His	D-Phe	Arg	Trp	Lys]	-NH ₂			
D-Tyr-MTII	SEQID No 4				Ac-	Nle	c[Asp	His	D-Tyr	Arg	Trp	Lys]	-NH ₂			
RMI-2001	SEQID No 5	Ac-	Ser	Tyr	Ser	c[Cys	Gly	His	D-Phe	Arg	Trp	Cys]	Lys	Pro	Val	-NH ₂
RMI-2004	SEQID No 6	Ac-	Ser	Tyr	Ser	Nle	c[Asp	His	D-Phe	Arg	Trp	Lys]	Gly	Pro	Val	-NH ₂
Nle-Y-MSH	SEQID No 7		Ac-	Tyr	Val	Nle	Gly	His	Phe	Arg	Trp	Asp	Arg	Phe	Gly	-NH ₂
SHU9119	SEQID No 8				Ac-	Nle	c[Asp	His	D-Nal	Arg	Trp	Lys]	-NH ₂			
RMI-2005	SEQID No 9				Ac-	c[Cys	Gly	His	D-Nal	Arg	Trp	Cys]	-NH ₂			

Table 2

LIGAND	MC3R		MC4R	
	KI	EC50	KI	EC50
α -MSH	9,40 \pm 3,17	11,6 \pm 3,2	9,17 \pm 4,23	1,34 \pm 0,50
NDP-MSH	1,19 \pm 0,51	0,309 \pm 0,170	3,14 \pm 1,18	0,0927 \pm 0,0471
MT-II	4,77 \pm 2,13	0,780 \pm 0,173	1,74 \pm 0,77	0,0111 \pm 0,0043
D-Tyr-MTII	204 \pm 87,2	20,3 \pm 7,1	3,84 \pm 0,83	0,466 \pm 0,189
RMI-2001	4,96 \pm 1,06	2,22 \pm 0,50	0,260 \pm 0,098	0,0300 \pm 0,0131
RMI-2004	1,23 \pm 0,13	3,86 \pm 0,92	4,51 \pm 0,99	0,326 \pm 0,155
Nle- γ -MSH	1,44 \pm 0,26	1,26 \pm 0,10	77,5 \pm 37,7	11,0 \pm 3,92
SHU9119	0,879 \pm 0,170		0,238 \pm 0,060	
RMI-2005	4,56 \pm 1,30		0,485 \pm 0,169	

CLAIMS

1. Use of any of the peptides
 - (i) Ac-Nle c[Asp His D-Tyr Arg Trp Lys]-NH₂;
 - (ii) Ac-Ser Tyr Ser c[Cys Gly His D-Phe Arg Trp Cys] Lys Pro Val-NH₂;
 - 5 (iii) Ac-Tyr Val Nle Gly His Phe Arg Trp Asp Arg Phe Gly-NH₂;
 - (iv) Ac-c[Cys Gly His D-Nal Arg Trp Cys]-NH₂; and
 - (v) Ac-Ser Tyr Ser Nle c[Asp His D-Phe Arg Trp Lys] Gly Pro Val-NH₂,for the manufacture of a composition for the therapy of a disorder in which melanocortin receptors are implicated.
- 10 2. Use according to claim 1, wherein the disorder is neurological.
3. Use according to claim 1, wherein the disorder is behavioural.
4. Use according to claim 1, wherein the disorder is cardiovascular.
5. Use according to claim 1, wherein the disorder is metabolic.
6. Use according to claim 1, wherein the disorder is sexual dysfunction.
- 15 7. Use according to claim 1, wherein the disorder is nerve damage caused by other therapy.
8. The peptide (i), (ii), (iii) or (iv) defined in claim 1.
9. The peptide (iii) defined in claim 1.
10. A peptide according to claim 8 or claim 9, for use in therapy.

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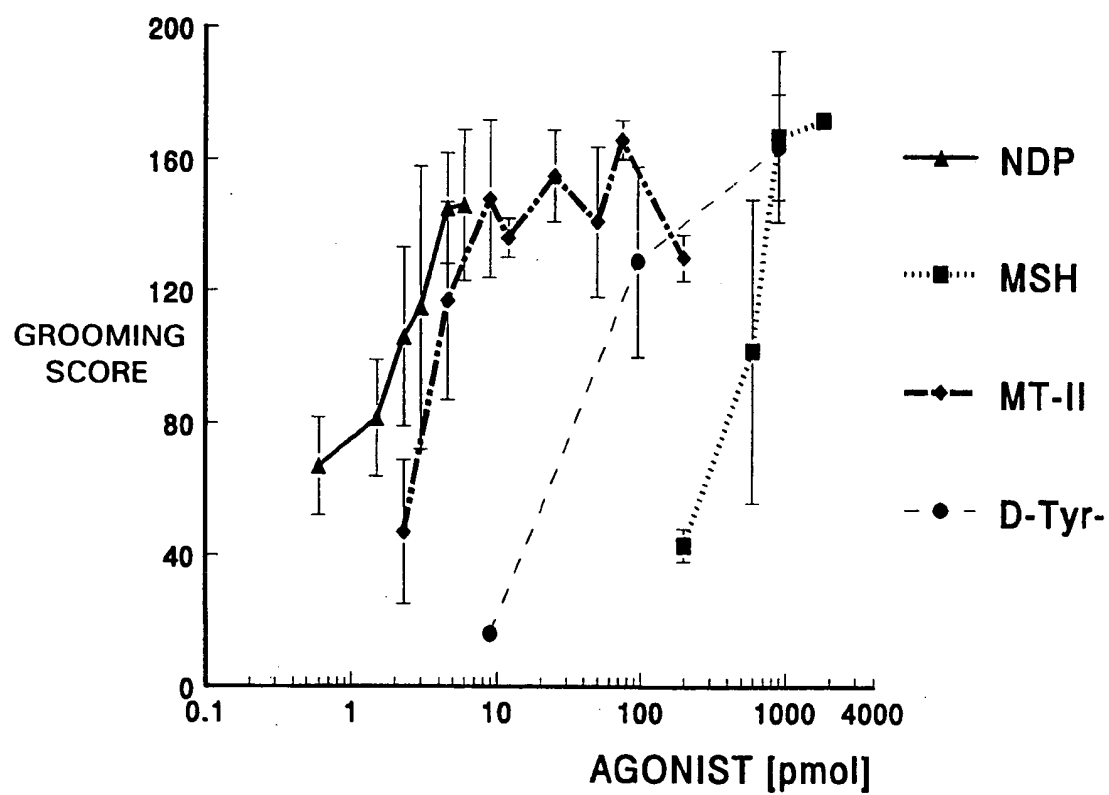


FIGURE 1a

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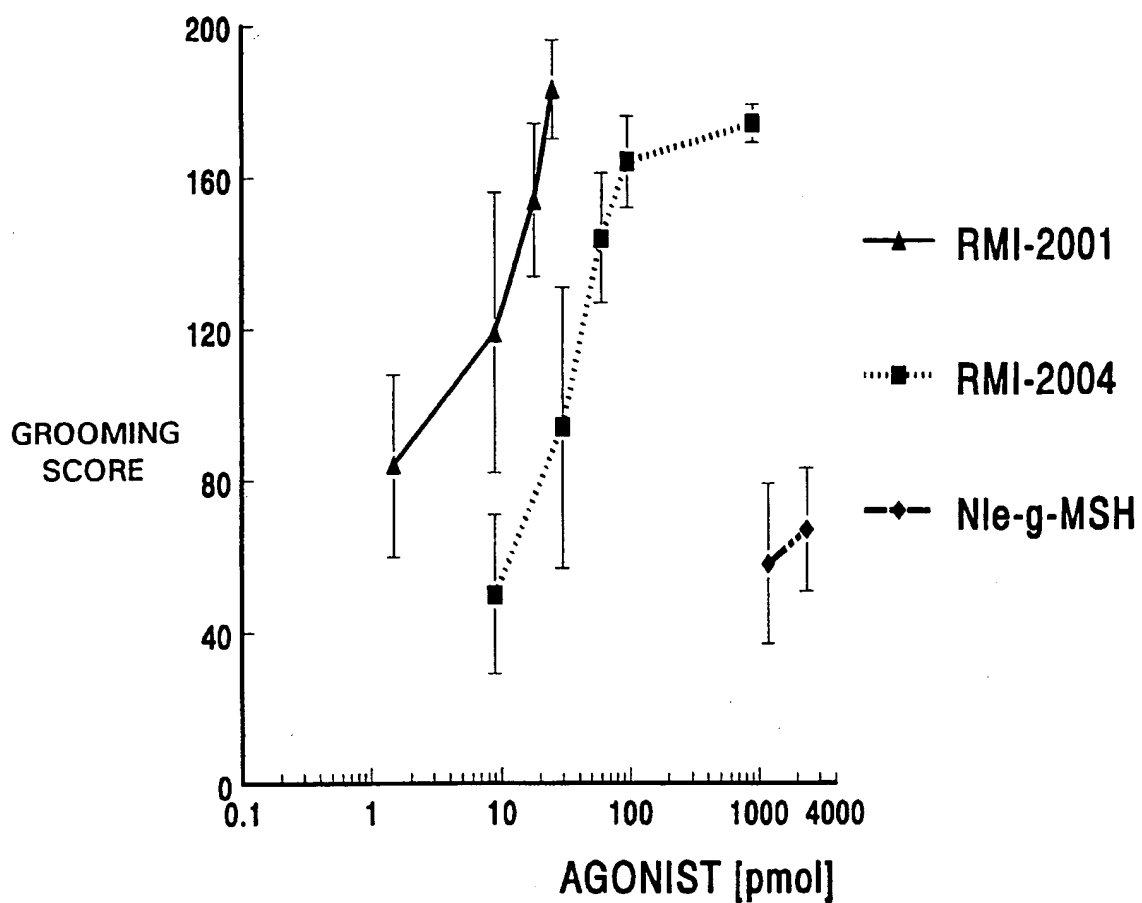


FIGURE 1b

INTERNATIONAL SEARCH REPORT

In ternational Application No

PCT/GB 99/01195

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K14/68 C07K14/685 A61K38/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PENG E.A.: "Binding and biological activity of C-terminally modified melanocortin peptides" PEPTIDES, vol. 18, no. 7, 1997, pages 1001-1008, XP002113015 See especially compound no 17 ---	1-10
X	US 5 731 408 A (HADLEY MAC E ET AL) 24 March 1998 (1998-03-24) see especially Tab III ---	1-8,10
X	US 5 674 839 A (AL-OBEIDI FAHAD ET AL) 7 October 1997 (1997-10-07) cited in the application See especially tables columns 4-6 --- -/--	1-8,10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	SCHAAPER E.A.: "Synthesis of cyclic alpha-MSH peptides" LETTERS PEPTIDE SCIENCE, vol. 5, no. 2-3, May 1998 (1998-05), pages 205-208, XP002113016 the whole document	1-8, 10
A	----- SCHIÖTH E.A.: "Selectivity of cyclic 'D-Nal-7! and 'D-Phe-7! substituted MSH analogues for the melanocortin receptor subtypes" PEPTIDES, vol. 18, no. 7, 1997, pages 1009-1013, XP002113070 the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/01195

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see FURTHER INFORMATION sheet PCT/ISA/210

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10 (partially)

Peptide i and its use

2. Claims: 1-10 (partially)

Peptide ii and its use

3. Claims: 1-10 (partially)

Peptide iii and its use

4. Claims: 1-10 (partially)

Peptide iv and its use

5. Claims: 1-7 (partially)

Use of peptide v as defined in claims 1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No

PCT/GB 99/01195

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